MANAGEMENT OF SEVERE MALARIA

Plenary Presentations

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Summary Report

PLENARY PRESENTATIONS

Overview of Clinical Malaria in Africa

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If one goes to practically any hospital in large areas of Sub-Saharan Africa and asks - What is the commonest disease? Or what is the biggest problem? The answer will invariably be "malaria".

Data collected in the early, descriptive stages of a series of studies carried out in collaboration between the Kenya Medical Research Institution and the Wellcome Trust at Kilifi shows the relative importance of malaria as a cause of death in inpatients in Kilifi hospital on the coast of Kenya.

Despite over 100 years of scientific investigation, there has been relatively little empirical description of the disease particularly among children, who take the brunt of *Plasmodium falciparum* infection. This has changed over the last decade or so, during which time a number of groups throughout Africa, all of which are represented at this Congress, have gradually built a fairly comprehensive picture of the clinical and epidemiological features of the disease. During this talk I will attempt to provide an overview of our current understanding of severe malaria in African children and to draw some attention to some of the new insights that have emerged.

Why is it necessary to understand the underlying disease processes rather than take the simplistic view that all that is needed is an adequate supply of anti-malarials?.

The majority of children who die do so within the first 24 hours (up to 80%) and many within 12 hours. Even the most effective antimalarials are unlikely to abort the progression of disease at this stage, and reduction of case fatality is likely to depend on building up a clear understanding of the pathophysiological processes at work and developing appropriate therapeutic approaches.

You cannot broach the problem without definitions. Hence in the early 90's a working party of experts developed for WHO such a definition. The point of presenting it at this stage is simply to illustrate the fact that it is a complex definition based on a mixture of clinical and laboratory observations, some of which cannot be made in the average hospital where malaria is a problem. Note too that this definition was not the result of an empirical study but represents expert views, derived mainly from experiences of non-immune adults from South East Asia. This is not to detract from its value. Indeed this kind of definition is essential for detailed research studies and is being revised. However, a simpler definition or classification would be more useful for many clinical and epidemiological purposes.

At Kilifi district hospital we have tried to develop a simplified way of looking at the clinical spectrum of severe malaria. By examining about 1800 consecutive admissions to the paediatric ward with a primary diagnosis of malaria. Admission policy was determined by ministry of health clinical officers not connected with the research unit. Thus this probably captures reasonably well the spectrum of disease admitted to many such hospitals.

A couple of points deserve emphasis:
The first is that three clinical syndromes account for the majority of deaths - Impaired consciousness (coma), anaemia and respiratory distress. I will elaborate later on what these syndromes comprise.

The second is that, although severe anaemia accounted for the largest group in terms of numbers, the actual case fatality is those who did not overlap with the other groups was relatively low (1.3%).

Finally, and worth our attention, is that from the point of view of severity as defined by outcome, children who present with an overlap of the syndromes, especially that between coma and respiratory distress, have a very high case fatality.

Thus the complexity of severe malaria is this setting can usefully be simplified into three overlapping but reasonably distinct clinical syndromes.

First, **severe malarial anaemia in isolation** , that is when a child is asymptomatic, it is numerically common but with a relatively low case fatality rate, requiring in most cases conservative management and not necessarily blood transfusion.

It is arbitrarily defined as a haemoglobin of less than 5 grms in a patient with a parasitaemia in excess of 10,000 trophozoites per cubic millimeter, with normocytic indices. The problem with such a definition is that parasitisation is common in malaria endemic communities and anaemia is multifactorial, - so that the occurrence of both does not necessarily mean cause and effect. However, it is striking that the incidence of the syndrome, even when defined in this way, closely parallels the incidence of other forms of severe malaria in areas where there is distinct seasonality.

It is predominantly a manifestation of disease in young children (less than 2 years) and we shall refer back to this when discussing some aspects of differences in disease patters in relation to transmission intensity.

Children with severe anaemia who present in respiratory distress and or impaired consciousness are along a more critical spectrum of disease.

Which leads us on to discuss **respiratory distress** . Surprisingly, respiratory disease does not feature in textbook descriptions of severe malaria, yet it is in this group of children that the case fatality is in fact highest. There are many reasons why a child with severe malaria might have respiratory distress. I am going to summarise much research by saying that in the majority of cases respiratory distress is the clinical manifestation of a severe metabolic acidosis.

A total of 238 consecutive children with severe malaria were grouped into i.) no respiratory distress, ii.) respiratory distress, but survived, and iii.)a respiratory disease and death. The degree of metabolic acidosis is measured by the base excess, given as a negative value. Normally, the concentration of hydrogen ions is maintained in very tight bounds by homeostatic mechanisms and the normal base excess is +/- 4. It can be seen that a metabolic acidosis is a common feature of severe malaria and that in children in respiratory distress it is very severe, and even more so in those who die. The underlying reasons why children with severe malaria develop a metabolic acidosis may be complex, but two factors dominate: hypovolaemia from dehydration and severe anaemia, resulting in reduced oxygen-carrying capacity to tissues. This has a number of important implications for the management of severe malaria in children which will be outlined in the next talk, and detailed discussion will take place in the breakout session.

I want to turn now to **coma** , which for the purposes of this presentation, may be taken to be synonymous with the generally used term "**cerebral malaria** ". The classical understanding of cerebral malaria, and one which still seems to underpin quite a lot of thinking and *in vitro* experiments relating to pathogenesis, is based on the histopathological picture illustrated here.

In post mortem samples you can see cerebral vessels packed with sequestered red cells containing mature parasites. When one sees this appearance in the brain of someone who died having presented in coma, it is perhaps a natural conclusion to regard the microvascular

obstruction as the defining feature of the clinical syndrome. However, emerging experience from a number of clinical studies suggests that this is an incomplete picture and that cerebral malaria is not a homogenous condition but a collection of syndromes where different pathophysiological events end up in the same clinical manifestation - coma.

Drawing out these distinctions is important because they have implications for both the management of children with cerebral malaria and for those trying to understand the detailed pathogenesis.

I want to illustrate the four distinct scenarios which converge to produce the same apparent syndrome of which should be familiar to anyone managing children with cerebral malaria.

The first child presents with a history of seizures, possibly one but more typically several, prior to admission to hospital in coma. The child may in addition have few or none of the known poor prognostic factors - such as hypoglycaemia or acidosis. Treatment will usually be initiated with parenteral anti malarials and maintenance fluids. Recovery of consciousness is fairly rapid occurring within 8 hours. It appears that in these children coma is due to an abnormally prolonged post-ictal state. The reasons for this are not yet clear, and though *Plasmodium falciparum* does appear to be epileptogenic, it is difficult to believe that this short-lived syndrome is caused by the classical histophathological picture seen earlier.

The second child may or may not have a history preceding the seizures, but is also brought to hospital in coma. On careful examination, the child may be noted to have one or more of several subtle signs - including irregular breathing (these children often are markedly hypoxic), increased salivation, or nystagmoid eye movements. Cerebral function monitoring or EEG, which is of course not possible in any but the most specialised units, shows that these children are in covert status epilipticus. When given anti-epileptics, they usually recover consciousness over few hours, sometimes with startling rapidity. In a busy hospital ward, these subtle signs may be overlooked as the child is considered to have cerebral malaria. The natural history of this syndrome if not aborted with antiepileptics is not know and one can imagine death ensuring from hypoxia without house in attendance being award that a simple and easily available manoeuvre could make a dramatic difference. Though we do not understand the trigger for the status it is again difficult to reconcile the rapid recovery of this syndrome with the pathology considered typical of cerebral malaria.

The third child presenting in coma may or may not have seizures but on admission, is noted to be having deep breathing - kussmuauls breathing. Where facilities exist, blood gas measurements will show the child to be markedly acidotic. In addition, the haemoglobin may be low, the blood glucose subnormal, and the electrolyte profile abnormal. If vigorous attention is given to the metabolic derangement, the child may again recover consciousness over a few hours. The coma seems to be possibly a protective response to metabolic stress which, when received, results in normal function.

You may by now be wondering whether there is such a thing as cerebral malaria, as typically understood - that is, a primary neurological condition lesion where the primary neurological condition lesion where the primary pathology is in the brain.

The fourth child is one who presents in coma, with or without any of the complications mentioned in the other three scenarios. Despite appropriate management, coma persists for a longer period, between 24-72 hours and, although many recover fully, there is a significant incidence of neurological sequelae, perhaps not when one sees the kind of damage that can be done. A CT scan of such a child, taken some months later, shows extensive brain atrophy.

I hope I have illustrated that a clinical syndrome previously considered a single entity, when subjected to clinical research, actually is more complex. That this complexity is not only relevant from the point of view of management, but also in the attempt to unravel the pathogenesis, the differences are worth bearing in mind.

Up to this point I have attempted to provide an overview of the clinical spectrum of severe malaria in African children. The data has been derived mostly from a specific research unit in Kilifi where I have been involved in clinical studies for a number of years. Similarities emerge in an increasing number of studies from different settings across Africa. But it would be incomplete in a discussion of the clinical spectrum of severe malaria, not to mention some variations in the clinical picture under different transmission conditions. Many of you will be aware that the whole issue of differences in morbidity and mortality with differing levels of transmission has been an extremely contentious issue over the last few years. I have no intention of straying into this debate as the main protagonists are here at this congress and I will have to leave it to them to argue it out. However, there are probably some reasonably uncontroversial points relevant to this discussion.

We have compared the age distribution of children admitted to hospital with malaria in two differing transmission settings - Kilifi, an area of moderate transmission, and Ifakara in Tanzania, an area with considerably higher transmission. The striking observation is that in Ifakara, the concentration of disease is in very young children and consistent with the earlier age distribution profile of severe disease, there is a relatively higher proportion of severe malarial anaemia in Ifakara compared to Kilifi. Where transmission is high, as in Ifakara, children on average will encounter malaria at an earlier age, compared with children in a lower transmission setting.

Interesting data comes from comparing the relative amounts of severe anaemia and cerebral malaria reported in a number of clinical descriptive studies from different sites over Africa. The sites are arranged from left to right in order of increasing transmission density. From Dakar in Senegal, with the lowest level of transmission compatible with stable endemicity, to the very high transmission levels seen around Lake Victoria in Kenya. The relationship is not absolute but this data does show that, whilst the clinical spectrum I have described may be generalised, one can expect local differences in the relative importance of a given syndrome.

In this talk, I began with a useful but complex definition of severe malaria. I moved on to a simpler one based on three main clinical syndromes. There are a number of important pathophysiological processes such as hypoglycaemia and impaired renal function that I have not addressed because their impact is captured in the broader approach we have taken.

I want to finish by emphasising the importance of bed side clinical signs. We have examined the ability of various diagnostic groupings to identify those at risk of dying. The combination of two signs - prostration (inability to sit or feed) and any degree of respiratory distress - forms a clinically useful classification.

For those of us who find themselves faced with yet another season of malaria, at a busy rural hospital, with minimal facilities - this is a practical classification that identifies the children who need attention. The critical signs to identify those requiring attention are prostration or respiratory distress. Clearly, prostration will include all children in coma as well as quite a number with lesser degrees of impairment. The presence of signs often considered to be of major importance - severe anaemia or seizures - do not, on the basis of what now amounts to experience in managing thousands of children, constitute a high risk per se. But because a minority will deteriorate, they too need to be managed in hospital. Children lacking in any of these signs may safely be managed as outpatients.

In closing, although we have concentrated on malaria, in practice, children do not present at health facilities so neatly labelled. But this kind of approach can, with minimal modification fit the integrated management of childhood illness approach.

Management of Severe Malaria - Implications for Research

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Introduction

It is tempting, following a talk that beautifully summarises recent clinical research on malaria, to move straight on to look in more detail at some of the emerging data on severe malaria and to consider what are the potential priorities for clinical research. But particularly in this unique meeting, it is important to take a step back and look at the overall context in which clinical research takes place. Therefore in the next few minutes, I will first briefly consider the process and requirements for clinical research. I will then, in the second half of my talk, review some of the areas where research could make a difference. While I am doing this, I will also flag up areas which will be considered in more depth at the breakaway sessions of this congress.

What's happening now?

The first thing to say is that research on severe malaria is research on failure- failure to prevent malaria and failure to treat it quickly and appropriately when it occurs, well before a hospital is required. In view of this, I am in no doubt that the *fundamental* research priority lies in these areas. Why then do we continue to do research on severe malaria at all? The answer is that even if the most optimistic targets of us all are met, it is still the fact that a very large part of the clinical load facing health care professionals throughout Africa for the next twenty years (at least) will continue to be severe malaria. That being the case, it is very sobering to reflect on how much clinical research has had any real effect on practice in the ordinary hospitals all over Africa that deal with severe malaria on a day to day basis.

Have there really been any major improvements in the past ten, or even twenty years? I wonder how many of us even know what is really going on in these hospitals - what is the case fatality of severe malaria in ordinary, non-research hospitals across Africa? And yet, unless we know what is going on, and probably more importantly what is not happening, we start from a pretty unrealistic position if we want our research to have a real impact. In saying this, I do not simply mean what is happening in technical terms e.g. Can blood sugar be measured? What is the fluid policy? But what is happening in terms of staffing, morale, training and all the other things that have an impact on the care of severely ill children? Of course, one of reasons why we often don't have a clear picture is that this kind of research, whether one calls it audit or operational research or applied health systems research, is very difficult. Unfortunately, it is also seriously unattractive: there are not many papers in Nature or the New England Journal to be had from it. This has to change, or otherwise we really have no basis on which to develop strategies for clinical research which stand a chance of affecting practice.

Research Requirements

Once one knows what is happening, the second requirement is to have a good research infrastructure to generate ideas and act as a test bed to establish which ones are promising - and it is perhaps worth saying a few words about this. The issue of *sustainable* funding for research centres in Africa has already been dealt with extensively, indeed it is part of the whole rationale for this meeting, but it won't hurt to say again that this is an absolute requirement. Related, and as important, is the issue of developing critical mass. This is important for capacity building, but also for raising the intellectual temperature and rigour. No area of science can afford to be happy with just ticking over, but given the scale of the problem we deal with, we more than most simply cannot afford to be carrying out poorly thought-out studies, or rediscovering wheels. With the best will in the world, it really is very difficult to see how much progress can be made by isolated researchers in small groups with precarious funding.

A further requirement is that research at this stage is closely tied in with ministries of health and the national control programmes. There needs to be a degree of involvement or ownership. If this is not established it will be an uphill task to promote policy changes further

down the line. In saying this I am not advocating a prescriptive attitude: to my mind the tension between so called "directed" research and "imaginative" or curiosity driven research is meaningless. What is important is to have short-, medium- and long-term strategies, and to know which is which. Short-term strategies will necessarily be more concerned with immediate realities, while long-term strategies may involve a large degree of speculation, the applicability of which may not be immediately apparent. We have to be clear which is which: we should not kid ourselves that finding out which *var* genes are transcribed in a particular clinical syndrome, to take something which I would very much like to know, is going to have much impact over the next few years in the hospital in which we do the research.

Testing the fruits of research

Having generated good ideas, such as a promising ancillary treatment for cerebral malaria, a new regimen for quinine or whatever- the next requirement is to know quickly and definitively whether or not it works, and what it costs. We cannot afford to go on repeating studies which are just not quite big enough to be sure, nor powerful enough to convince policy makers. Of course, this is in no way a problem restricted to Africa, and the answer is in one sense simple: numbers, numbers, numbers. There has been a remarkable movement over the last fifteen years or so to ever bigger studies in clinical research in general but there are some particular problems that we face in Africa. For a start there are just not enough centres which can participate in such studies, given that they require a minimum in terms of infrastructure and personnel. The development of a research network for severe malaria through a MIM initiative is a very promising development, but we should not be complacent as problems remain. First, we have to recognise that whatever the altruistic motives of researchers, and I believe that in this area there *is* a very high level of humanitarian commitment, we cannot get away from the fact that there is a tension between the need for individuals and research groups to maximise their research outputs, and the desire to pool resources. In a nutshell, which would you rather have: a first author paper in the Lancet describing a ***promising*** reduction in coma resolution time in cerebral malaria, or be listed in the acknowledgements, with 48 others, in a ***definitive*** study of 2000 children which show that it was a fluke and that the intervention is useless? If we can solve this problem, and I think we can so long as funders really take it on board, there remains the concern that by their very nature the few sophisticated research units in Africa are really very untypical of the average under-resourced district hospital. What we really need is an approach that can mount large simple outcome trials in a network of such hospitals and this presents a formidable challenge.

Translation and sustainability

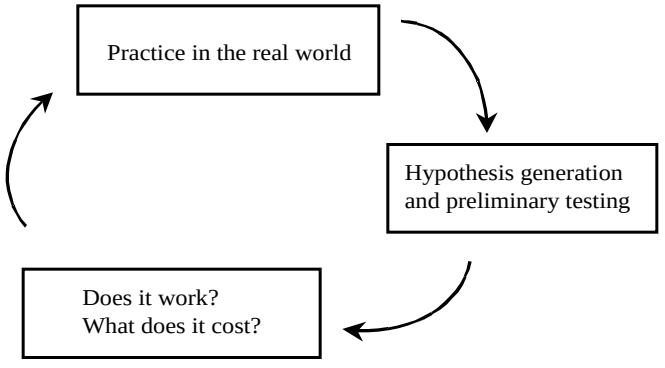
Finally having established that "wonderquin" at only 5 cents a dose can reduce case fatality by 20 %, we come to the real crunch issue: the translation of the research findings into practice. As researchers we tend to have a poor grasp on what is required. The first mistake we tend to make is the idea that there is ***a person*** in the ministry of health to whom it is only necessary to explain our most recent findings in order to change practice throughout the land. When this does not happen, as of course it never does, we complain that no one seems very interested in our findings. Of course the truth is that there is no such person. The whole process of policy formation and implementation is enormously more complex involving many individuals and groupings at different levels, within different departments and with many different priorities, all very pressing. Worse, many of the key parts of the chain are not in the ministry of health, but in other sectors such as finance, where decisions are taken on budgets for procurement etc.

Does this mean that all researchers have to engage in learning the arcane rules of the civil service and spend countless hours sitting outside the door of the permanent secretary? No, of course it would be a waste of time for us all to be doing this, but it is important that the research community and all other stake holders in health policy, find way of working together from an early stage if we are to avoid years of frustrating delay.

The second mistake we tend to make is to carry over our concept of ourselves as *malaria* researchers, researching on malaria. In the real world children do not turn up at health facilities neatly labelled as malaria, but as sick children in whom malaria may or may not be a major factor. It is important to realise that translation of research about malaria into useful

practice often involves a broadening of the approach, this is why the Integrated Management of Childhood Illness (IMCI) is such an important and central concept. The Division of Curative Services may sometimes be a more important target for ones networking than the national malaria control programme.

There are many reasons why perfectly good research does not end up being translated into practice, from failure to convey the information to the right people to problems at the other end of the line where hard pressed demoralised staff treat sick children. This brings us back to where we started, with the need for health systems research and operational research. The perspective which I have been trying to capture is shown in the Figure below, with a continuous interaction between what is happening, what could in theory be done, demonstrating that it works and is affordable and then translating it into practice and seeing its effect.



Room for Improvement?

So much then for the broader perspective - but all this does presuppose that there ***are*** things which clinical research can generate which will improve the outlook for children with severe malaria

Table 1 is taken from the soon to be published revision of the WHO guidelines on severe malaria. It is a list of interventions for severe malaria that have been suggested, but for which there is no evidence to support their efficacy. That does not mean that they are all useless - some may yet turn out to be important - but as yet, despite the fact that most have been talked about for many years, there is no evidence to support their use. One can look at this in different ways: a pessimist might say that there is not much chance of the next on the list doing much better, while an optimist would say we must find one that works soon!

Table 1: Cerebral Malaria: ancillary treatments not recommended

1.	Corticosteroids
2	Other anti-inflamatory agents
3	Other anti-cerebral oedema agents
4	Low molecular weight dextran
5	Adrenaline
6	Heparin
7	Prostacyclin
8	Oxypentifylline
9	Hyperbaric oxygen
10	Cyclosporin A
11	Hyperimmune serum
12	Iron chelators
13	Dichloroacetate
14	Anti-TNF antibodies

One thing that one notices from the list is that many of these drugs would not be found close to hand in an average hospital. Now this of course may not matter, but it does raise the issue of whether we are happy that the things we do have available are being used in an optimum way? One might hope that this is the case because, after all, there are only very few

interventions available to us which can truly be described as potentially life saving and it ought to be possible to use them properly. These are listed in Table 2, and in fact with the addition of oxygen this would pretty much be the key list of things that could make a critical difference to any very sick child in a district hospital, whatever the diagnosis.

Table 2 Treatments available in most hospitals and potentially of major importance in severe malaria

1. Antimalarials
2. Antibiotics
3. Sugar
4. Fluids
5. Blood
6. Anticonvulsants
7. Antipyretics
8. Common sense

What I want to do now is run briefly through a few examples from this list and try to convince you that, far from all being sorted out, there are a large number of key research issues that need tackling. One of the things that did strike me in being involved with the preparation of the breakout sessions on severe disease for this congress, was the dearth of submissions on central and very difficult issues of practical management. In saying this, it is important to stress that I am not presenting a sort of Luddite argument that we should limit our research strategies to such a list. At Kilifi we have our fluorescent-activated cell-sorter and PCR humming along as enthusiastically as in any other research centre. Nonetheless, I do think there is a risk of going for some areas of research because, basically, they are easy. It is easier for instance, to measure the levels of the latest cytokine in a nice clean laboratory, than to concentrate on the messy and difficult business of looking after sick children in hot overcrowded and under-resourced hospital wards.

Anti-malarials

One might think there is not a lot to say here. Quinine is the standard treatment, it is widely available, we have a lot of experience and resistance is not yet a problem with it: But resistance will come, quinine is not an innocuous drug and it is far from clear that we do have treatment regimes absolutely right.

The previous talk stressed the speed with which children die of malaria and yet quinine is rather a slowly acting drug. This is one of the things which make the qinghasou /artemesinin group potentially very attractive as alternatives to quinine. Those who attended the breakout on Monday will have heard Nick White present the meta-analysis of the artemether-quinine trials. The basic message is that artemether is about as good as quinine. Some people have been rather disappointed at this, hoping that it would be dramatically better, but I would argue that it is pretty good news to have a new group of potentially affordable drugs that are as good as one of the most important drugs we have. I think there is also a strong argument that we may have somewhat loaded the dice against artemether by doing trials in patients with cerebral malaria. On the face of it, it makes sense to test your most exciting drugs in your most dramatic cases, but there is a strong argument that we should now be looking at the use of these drugs earlier in the story. The other new slant is that many people now feel that there are strong reasons for thinking that artesunate may have quite major advantages over artemether, and if such trials are to be carried out it will be necessary to develop the sort of multicentre facility discussed above.

Antibiotics

Next on out list is antibiotics and one might wonder why are we talking about antibiotics to treat malaria. Our recent experience in Kilifi is that a significant proportion of children with severe malaria also have concurrent bacteraemias and that this syndrome is associated with very high mortality. This a potentially very important management issue. It also presents interesting ethical issues: should we do randomised trials if observational studies reveal something for which we already know we have a treatment in broad spectrum antibiotics?

Our feeling at Kilifi is that our local data is so convincing, at least to us, that we now treat all children under three years who have severe malaria with broad spectrum antibiotics. Clearly this whole story needs to be sorted out: is the same true elsewhere, and what is the optimum management?

Sugar

One of the cheapest and most widely available life-saving interventions for malaria is sugar. Hypoglycaemia is strongly associated with death. It is also a major risk factor for neurological sequelae and for cognitive deficit, even in children with no obvious sequelae.

In most series of children with severe malaria, around 15% have hypoglycaemia on admission. However, something less well appreciated is that other children who are normoglycaemic on admission often develop hypoglycaemia despite routine 5% dextrose as part of management fluids. More worrying in our experience is that children already known to have been hypoglycaemic and who have received 50% dextrose and then maintenance with 10% dextrose still commonly develop recurrent hypoglycaemia. This data is from a setting where we can afford to monitor glucose regularly and at any deterioration. Most hospitals are not able to provide regular and quick measurements. Glucose sticks are the obvious answer, but they are prohibitively expensive. Thus it seems certain that one of the most important complications of severe malaria is often not recognised or managed.

There is no simple answer to this problem. Some have suggested using sugar solutions through nasogastric tubes as a potential approach. This initially has the feel of being good practical sense, but the problem of recurrent hypoglycaemia, while receiving intravenous dextrose, suggests that it is unlikely that one could keep up with demand by this route. Testing nasogastric regimes presents some interesting ethical problems: hypoglycaemia is considered by most people to be an emergency, given its potential for brain damage. Any research centre that can measure levels quickly enough in a kinetic monitoring of nasogastric glucose will certainly be well set up to give definitive intravenous treatment. Can it be justified to delay this? But if not then how can one ever be sure of the safety or efficacy for recommendations to be used in less optimum conditions? Hypoglycaemia is one of the most important problems we face and so far as I can see there are no easy answers. It does, however, seem that there is something wrong with our perspective when this congress did not receive a single abstract on this issue- a major cause of death and sequelae for which the treatment is cheap and widely available.

Blood

In the previous talk it was clear that the overlap of anaemia and respiratory distress is a common situation associated with a very high mortality, for which relatively cheap and widely available treatment – blood - is available. So what is the issue here? If one looks at protocols, where they exist, or talks to clinicians across Africa, there remains almost unanimity on the idea that transfusions in these pale breathless children should be given very slowly, minimising volume by the use of packed cells and further by the use of diuretics. The reasoning, hallowed by generations of repetition, is that these children are in congestive cardiac failure.

However, we now know that the usual reason for these children being breathless is that they are severely acidotic. There is not time to explore here the pathophysiology of what is going on to make these children so severely acidotic, but I will summarise a lot of work by colleagues by saying that two major factors are anaemia and hypovolaemaia. Now, hypovolaemic acidosis is not unique to malaria: it is a common end stage presentation of many life-threatening conditions all over the world. The management of such children turning up at casualty or on intensive care units in Europe, America or here in Durban involves an absolutely key component: *rapid* resuscitation, often with large volumes of fluid. You will note that this is the exact opposite of what I have said is the practice in malaria, because the cause has been presumed to be different.

So we have a situation where we have diametrically opposite possibilities for the delivery of a life-saving intervention. If those who worry about congestive cardiac failure are right, then rapid resuscitation with blood will put the child at high risk of dying through volume

overload. If the scenario for the development of severe acidosis is right, then the traditional approach will fail to provide a life-saving treatment to the highest risk group. This would seem to be a pretty important research question, but again the congress received not a single abstract on the management of acute severe malarial anaemia. However, this seemed so important that we have arranged within this afternoon's session to have two presentations on this area.

Concluding Remarks

I want now to draw together and summarise what I have been saying. Firstly, I stressed that the really key issue is to prevent events getting as far as severe malaria. Despite this, we expect severe malaria to remain a massive clinical problem in African hospitals for many years to come. Therefore we need a strategic approach involving short, medium and long term strategies to reducing case fatality. I have concentrated on what could be called short-term research because I have argued there is great urgency for this. I have also argued that we have not been active enough in making what is actually happening now, in real hospitals across Africa, the centre point from which we set our research objectives. I have argued that there is a need for a much greater capacity to take promising interventions through to a definitive answer in short time, and subsequently that much greater attention to the process of translation of research findings into policy is required.

On the subject of what specific research can be expected to make a difference, I have steered clear of some approaches that might be considered more sophisticated or exciting (although I don't agree with this perception), and instead have concentrated on the really quite limited set of key options that may be life-saving in district hospitals. I have argued that in many, indeed I would say all, cases there are major unresolved research issues which, if not actually ignored, have certainly not received the attention they deserve. I hope that I have conveyed a sense that far from there being little that can be done, there is in fact an enormously important challenge for all of us here, whether we are researchers, policy makers or implementers. It has been a privilege to have the opportunity to share these thoughts and I feel very hopeful that the unique opportunities provided by MIM and a congress such as this will allow us to rise to this challenge.

BREAKOUT SESSIONS: MANAGEMENT OF SEVERE MALARIA

Programme

1. Management of Severe Malaria and Antimalarial Drugs : Joint Session
Chair: Dr. Pascal Ringwald and Dr. Piero Olliaro
Rapporteur: Dr. Didier Diallo, Dr. Dora Akinboye, Dr. Eric Achidi

Presentations (20 mins)
1. Implications of drug resistance and loading dose in treatment of severe malaria in Africa - Akintunde Sowunmi.
2. Current practices and Potential Role of antimalarial suppositories in management of severe Malaria in Rural Areas - Melba Gomes.
3. Meta-Analysis of arthemether and quinine trials in management of severe malaria - Nick White.

Abstracts (5 min each)
1. La quinine en solution intrarectale est efficace dans le neuropaludisme et les acces graves de l'enfant en Afrique - Hubert Barennes.
2. Artesunate suppositories in the treatment of moderately severe malaria in Malawian children - Madalitso Tembo.
3. A randomised, placebo controlled, double-blind study of the tolerability and efficacy of Artesunate plus sulphadoxine/pyrimethamine combinations vs. Single-agent sulphadoxine/pyrimethamine for the treatment of uncomplicated falciparum malaria - Lorenz von Seidlein.
4. Comparative efficacy of chloroquine and co-trimoxazole in acute uncomplicated falciparum malaria in children - Adegoke Falade.

2. Management of Severe Malaria II
Chairs: Professor Ogobara Doumbo, Dr Charles Newton
Rapporteurs: Dr Hubert Barennes, Dr. Mike English

1. Severe Malaria in African Children (SMAC) network - Terrie Taylor.
2. Evidence of moderate and severe brain swelling in paediatric cerebral malaria: an autopsy study - R.A. Carr.
3. Retinal findings as a prognostic indicator in cerebral malaria - Jeff Ajewole.
4. Phenobarbitone prophylaxis in childhood cerebral malaria - Jane Crawley.
5. Malaria – are developmental problems associated with severe disease? - Penny Holding.
6. Effect of Paracetamol on parasite clearance in Kenyan children with severe malaria - Faith Osier.
7. Bacteraemia complicating severe malaria in children - James Berkley.
   Discussion

3. Management of Severe Malaria III
Chairs: Dr Ayo Palmer and Professor P Kremsner
Rapporteurs: Dr Hubert Barennes and Dr. Mike English

1. The spectrum of severe malaria in The Gambia and its relationship to mortality - Stanley Usen.
2. Susceptibility of red blood cells from children with severe *Plasmodium falciparum* anaemia and age matched controls of erythrophagocytosis - John Waitumbi.
3. Binding of complement of C3d to erythrocytes is associated with anaemia in acute childhood malaria - Bamenla Goka.
4. Red cell deformability in severe malaria - Kevin Marsh.
5. Metabolic acidosis: the role of intravenous fluids and blood - Mike English.
6. Metabolic acidosis: the role of dichloroacetate - Sanjeev Krishna.

7. Discussion.

Summary Report: Management of Severe Malaria

The problem of severe malaria was explored in two plenary talks and two and a half breakout sessions. Two broad themes were addressed during the plenaries:

- a summary of the current state of the art in clinical research on severe malaria
- an examination of the role of clinical research in the broader objective of malaria control.

The breakout sessions provided the opportunity for short presentations on a wide range of specific clinical issues and wherever possible, it was attempted to set discussion in the framework of the wider perspective taken in the plenaries.

The main issues and themes to arise are summarised in brief below. A few useful overarching points are highlighted :

· Severe malaria indicates failure of control- an absolute priority is the early and appropriate treatment of febrile illness to prevent further deterioration. In this context, work on identifying affordable safe drugs, preventing the development of resistance by using combinations, and delivery to the point where most treatment takes place (the home) all require maximum support.

· Nonetheless, even with the most optimistic predictions of success, severe malaria will continue to form one of the single biggest problems at health centres and hospitals in Africa for the next twenty years.

· Therefore, a research strategy is required which includes short, medium and long-term objectives. The long-term objectives of better understanding the pathophysiology in order to develop new therapeutic approaches remains important, but it should be recognised that there is a dearth of information on how best to use even the few interventions that we have and that are known to be potentially life saving. This must be addressed with urgency.

· In order to do this it is important to know what is actually happening on the ground where the majority of cases are treated. This will define the agenda, at least for short and medium term research strategies.

· These should concentrate on taking promising approaches as quickly as possible from pilot stage to definitive study. Such studies will need to be large enough to produce convincing answers and avoid the need for repeated small trials. This will necessitate the formation of the capacity for carrying out multicenre studies both within and between countries

· Early and close collaboration with the appropriate divisions of Ministries of Health is essential if clinical research is to be translated into practice. In many cases, current levels of collaboration are too little too late and do not result in a sense of ownership for those individuals and groupings who will be charged with implementation. Although collaboration with control programmes is essential, it should also be recognised that the required emphasis on the sick child means that collaboration with other groupings, particularly those covering curative services, will be equally important.

Summary of main issues discussed

The following areas were some of those identified as either areas of relative ignorance or those requiring further development. Exploiting these areas will require active input from African scientists, the development of working links between them, and an increased level of communication at an early stage with policy makers. Policy makers themselves may do much to encourage the development of indigenous research by recognising its value, facilitating its execution and highlighting areas requiring attention.

- ***Description of disease:*** The heterogeneity of severe disease means that each country will require more detailed knowledge of its own current pattern and burden of disease since this may vary between different areas / countries. Ideally, this information should come from health facility based sources and the community. Such data will be invaluable for planning effective, appropriate control strategies (including resource allocation).

- ***Definitions of disease:*** Consensus definitions of disease syndromes may facilitate information sharing and understanding, and make the use of research information easier for policy makers.

- ***Malaria in the context of the sick child:*** Managing clinical malaria must be considered part of an overall approach to delivering effective treatment to sick children since malaria often overlaps with other diseases.

- ***Early treatment of mild / moderate disease:*** While the natural history of severe disease remains poorly understood, there is clearly a need to examine the possibility that early effective treatment at community / peripheral levels may reduce the burden of severe disease. New drugs (e.g. Artemsinin derivatives) and routes of administration (e.g. rectal) make this particularly pertinent.

- ***Pathogenesis of Disease:*** Many areas still remain poorly understood, perhaps most obviously (but not exclusively):
  The mechanisms resulting in coma
  The natural history of anaemia
  Why severe anaemia may take such dramatically different clinical forms
  Acidosis
  Hypoglycaemia
  Seizures / convulsions
  The development of neurological sequelae

- ***The long-term effects of severe malaria:*** In particular neuro-psychological sequelae and post discharge mortality and morbidity.

- ***The Ethical issues involved in research on severely ill children in Africa:*** Cultural heterogeneity may demand the development of locally appropriate approaches to these issues. In particular, the role of community consent and the need for individual consent / assent.

- ***The training of African clinical researchers:*** Including training in research at undergraduate and post-graduate levels as well as training in how to communicate research findings to the control community.

- ***Systems research to identify current strengths and weaknesses in management:***
  For example, the ability to deliver such interventions as safe blood for transfusion.

Improved understanding in all of the above areas might facilitate ***evidence based practice*** in malaria management and control. However, a key difficulty is the current in-ability of clinical researchers in Africa to test new and current approaches on the scale required to answer questions of true effectiveness. This is particularly important when the costs of different treatment strategies are being considered. Tackling this deficiency is a major but vitally important undertaking requiring multiple partners. The first steps of this process are being taken with:

The Severe Malaria in African Children (SMAC) Network
This network aims to develop:

- A working network of clinical researchers across Africa who might take part in large, simple intervention trials primarily with mortality as the outcome.

- The methodology required to undertake such trials.
- The infrastructure required to undertake such trials.

While the long-term nature of such a venture in Africa, a continent with major communication difficulties, poses particular problems, the need for such a structure is great. Basic research suggesting the usefulness of an intervention demands that its effectiveness be examined. In many cases this can only be achieved using a multi-centre approach, a lesson already learned in developed economy health-care systems. A particular challenge in Africa may be to develop the ability to test interventions at the level at which they must eventually often be used, the small hospital or health centre. This may require the development and testing of strategies that are simpler than those to be used in research centres. Examples of such interventions might include:

- The use of novel antimalarial drugs / formulations (including combination therapy)
- Protocols for intravenous fluid use and / or blood transfusion
- The treatment of hypoglycaemia

Afterword

A central theme to emerge in all of the above is the need to focus short and medium term clinical research on what is happening on the ground and on interventions that could make a real difference now. This will require high quality clinical research and trial design, but it will also require considerably more investment in health systems and operational research. One of the issues that funders will need to take on board is the inevitable tendency of the current scientific ethos to favour high profile publication. Thus, small studies of cutting edge therapies carried out by identified individuals win out over large studies of more mundane (but potentially more useful) approaches carried out by large collaborative groups (who do not receive much credit when their next grant renewal is due). It is difficult to see how clinical research in Africa can be given impetus along the lines described above, unless this fundamental issue is addressed.